

REMARKS

Regarding the Status of the Claims:

Claims 1-3, 6, 7, 12, 18, 22, 27, 29, 35, 42, 43, 48, 49, 56, 68, 74, 86, 90, 91, 121, 130, 132, 139, 153, 156, 178, 179, 181, 186, and 193-214 are currently pending for reconsideration. Of these, claims 1, 90, 121, 153, 186, 193 200, and 205 are in independent form.

Claims 1, 121, 195, 197-199, and 215 are currently amended. The amendments to claim 1 are intended to better highlight novel features of the invention. Claim 121 has been made independent, and claim 144 has been made dependent on claim 121. Amendments to the other claims have been made to correct minor errors noted during preparation of this communication or to improve the form thereof.

Claims 5, 13, 30, 74, 80, 81, 83, 105, 109, 111, 145, and 155-156 are canceled hereby. Claims 4, 8-11, 14-17, 19-21, 23-26, 28, 31-34, 36-41, 44-47, 50-55, 57-67, 69-73, 75-79, 82, 84, 85, 87-89, 92-104, 106-108, 110, 112-120, 122-129, 131, 133-138, 140-144, 146-152, 154, 157-177, 180, 182-185, and 187-192 were previously canceled.

Applicant reserves the right to prosecute all canceled claims in a continuing application.

Regarding the Objections to the Claims:

Regarding the objection that claims 195 and 199 are substantially duplicates of either other, claim 199 has been amended to recite that the wells are on the surface of the carrier.

Regarding the Rejection under 35 U.S.C. 112:

The Examiner has repeated the rejection of claims 43 and 48, and 214, under 35 U.S.C. 112, second paragraph. The basis for this rejection is not really understood. The Examiner seems to be treating the claims and the underlying description in the specification e.g., at page 30, lines 5-15 pertaining only to the structure of the wells. In fact, the claims in question pertain to the wells *and* the carrier and the relationship between the two. The text, in explaining the meaning of the term "juxtaposed" states that:

By juxtaposed is meant that in an area *where wells are found*, most of the area is well area and little of the area is interwell area.

A person having ordinary skill in the art would understand that the word "area" is referring the area of the carrier where the wells are located, and that "interwell area" refers to the space *between* the wells. Since the text clearly explains the meaning of the terms "area" and "interwell area", claims 43 and 214 are not indefinite.

Claim 48 is likewise directed to the wells and their relationship to the carrier. In the specification, the term "knife-edged" is defined as a limiting case of a substantially zero interwell area (see, e.g., page 30, lines 14-15). A person having ordinary skill in the art would understand this to be referring to the relationship between the wells and the carrier, and not just to the well structure.

Also in this regard, the Examiner is respectfully reminded that claim 48 recites that "a *rim* of a said well is substantially knife-edged".

To make even more clear that claims 43, 48, and 214 do not refer only to the wells, parent claim 1 have been amended to replace the two-part European format with a more straightforward, structure plus "wherein" format. It is respectfully submitted that when claims 43, 48, and 214 are read in the context of their amended parent claim, there is no longer any possible basis for the rejection.

Applicant respectfully traverses the rejection of claims 195 and 197-199 as being of improper form for failing to limit their respective parent claims. The Examiner asserts that these claims are directed to a method of making, but this is not correct. The preambles of all of these claims recite "A device".

Perhaps the rejection is based on the Examiner's interpretation of "formed" as being a method limitation. Although applicant does not agree that formed is necessarily a method limitation, the claims have been amended to substitute the word - - located - - for "formed". Withdrawal of the rejection is therefore respectfully requested.

Regarding the Rejections under 35 U.S.C. 103:

Claims 1-3, 6-7, 35, 42-43, 49, 56, 86, 121, 130, 132, 139, 145, 186, 193-197, 199-209, and 214 have been rejected as being unpatentable over Kim et al. U.S. patent publication 2003/0030184 in view of Bochner U.S. Patent 5,627,045 (Bochner) in light of Alberte et al. U.S. patent publication 2002/0052003 (Alberte). This rejection is respectfully traversed.

By way of background, Kim is concerned with the study of cell motility, and the apparatus and method disclosed therein are directed to achieving that objective. Those skilled in the art know that for a cell to migrate, i.e., to move under its own power, it must undergo a series of characteristic changes in shape (see figures below):

1. Extension of a lamellipodium or pseudopodium,
2. Adhesion of the extended leading edge to the substratum,
3. Translocation: forward flow (streaming of the cytosol), and
4. Retraction of the cell body to the substratum.

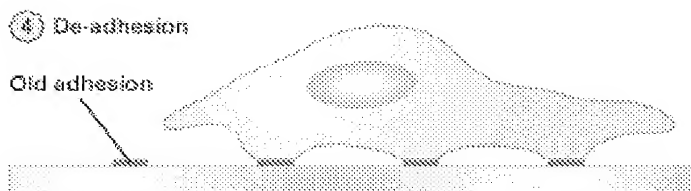
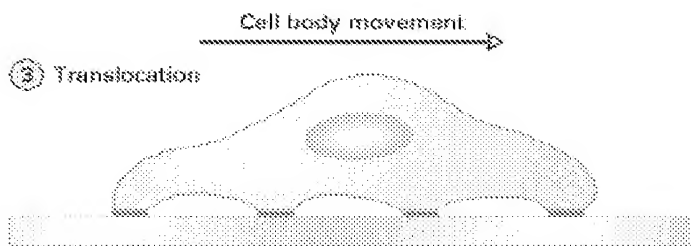
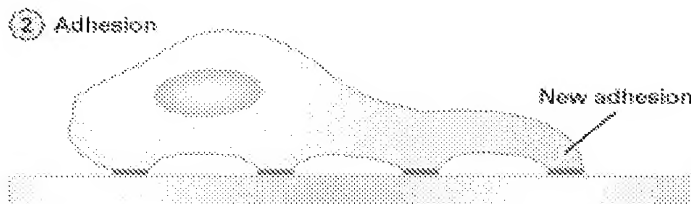
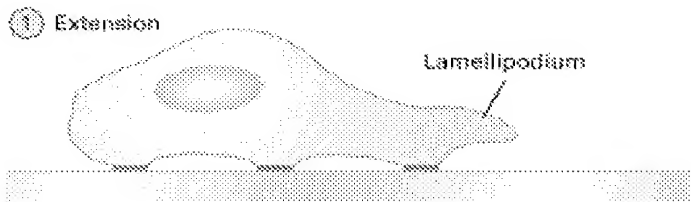
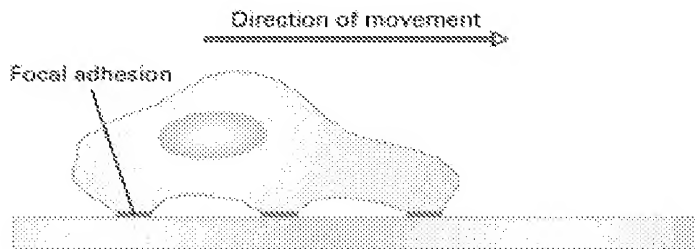


Figure 18-41. Steps in keratinocyte movement

As explained by *Lodish et al.*:

In a fast-moving cell such as a fish epidermal cell, movement begins with extension of one or more lamellipodia from the leading edge of the cell (step 1); some lamellipodia adhere to the substratum via focal adhesions (step 2). Then the bulk of the cytoplasm in the cell body flows forward (step 3). The trailing edge of the cell remains attached to the substratum until the tail eventually detaches and retracts into the cell body (step 4).

(From *Molecular Cell Biology*. 4th edition. *Lodish H, Berk A, Zipursky SL, et al.* New York: W. H. Freeman; 2000.)

A person having ordinary skill in the art would understand that for migration to occur, the cell must have a substratum to which its extensions can adhere. Likewise, there must not be any significant obstructions in the path of movement.

Kim's construction is designed to satisfy these requirements. Referring to FIGS. 1a and 1b, Kim provides a support 140 and a second layer 160 overlying the first layer. First layer 150 includes an array of micro-orifices 300 through which cells can be patterned, attached, or reversibly or irreversibly immobilized on the upper surface 140a of support 140.

Second layer 160 includes macro-orifices 170 overlying several micro-orifices. The macro-orifices 170 are arranged in a pattern or array through which test agents or solutions are deposited to contact cells that were previously deposited, attached, or reversibly or irreversibly immobilized to the upper surface 140a of the support 140 (see Kim, ¶ [0137]).

To provide the unobstructed surface on which the cells can migrate, layers 140 and 160 are separable from support 140 (see ¶ [0139]). These layers are lifted from support 140, ...or peeled away from the support when motility is to be observed.

Further, Kim describes a method for *attaching* cells onto a substrate by coating a flat support with a material that *causes adherence* of the cells to the substrate. The coating is provided by a stencil, i.e., a template/layer, having arrayed 'removed sections' (micro/macro orifices) (see Figs. 18, 27, 34; ¶¶ [0067- 0069], [0208], [0209], [0227], [0274], [0229-0235], [0238], [0240], [0242], [0244], [0254-0256], [0258], [0260-0262], [0264], [0281] [0285], [0287], [0290]).

Independent claim 1 as currently amended, recites that:

said wells are configured to prevent loss or migration of cells during storage, movement, testing *and observation*, and to *inhibit or delay adhesion* therein of living cells therein held in said wells.

From the description of Kim above, it is apparent that Kim alone does not satisfy either of these requirements, and the Examiner has expressly acknowledged this in the Office Action. In fact, by removing the first and second layers to allow observation of motility, Kim effectively dismantles the wells, thereby permitting migration, and by coating the substrate, Kim promotes adhesion of cells. In short, Kim teaches away from the structure of claim 1.

The Examiner seeks to remedy these fundamental deficiencies in Kim by reliance on Bochner in light of Alberte. The Examiner says she interprets Bochner as showing a gel cover that purportedly traps the suspended microorganisms, and, in the present Office Action, relies on it only for that showing. The Examiner is respectfully reminded that a rejection under 35 U.S.C. 103 must focus on how a person having ordinary skill in the art would interpret the reference.

Bochner is concerned with "providing suitable test media and methods for growth, isolation, and presumptive identification of various diverse organisms" (Col 6, lines 23-28) using standard, commercially available well-bearing devices. Organisms to be studied are suspended in a liquid gellable medium that is inoculated into the wells. This medium is then gelled to form a gel in which the organisms are evenly distributed (Col 9, lines 5-7).

A person having ordinary skill in the art would certainly not understand Bochner's organism-suspension gel as a cover, but rather a mechanism by which organisms to be tested are delivered to and held in Bochner's wells.

To treat Bochner's gel as a cover, and to suggest using it as cover for Kim's wells totally fails to take account of what Kim actually teaches. Nor do the Examiner's arguments demonstrate that a person having ordinary skill in the art would consider it obvious to use a gel as taught in Bochner on Kim.

A person having ordinary skill in the art would not get the idea from anything disclosed, taught or suggested in Bochner, or from anything else in his or her experience to modify Kim by inoculating the disclosed structure with a gellable fluid in which organisms to be studied are suspended, and to remove it along with the first and second layers. For one thing, if Kim's wells are covered, how would they be exposed to test

agents intended to be delivered through the macro-orifices. For another, how would the gel be removed with the first and second layers without removal of the cells to be observed? And if the gel is not removed, how can the cells migrate?

In short, it is clear that Kim teaches away from Bochner, and that following the Examiner's proposal would completely destroy Kim's utility for its intended purpose, i.e., to *permit* cell migration for motility study.

The Examiner further relies on Alberte, but there does not appear to be anything in this to remedy the deficiencies in Kim and Bochner. Alberte is concerned with anti-fouling compounds for ships and other marine equipment. The Examiner cites paragraphs 115 and 118 as relating to laboratory equipment, but applicant does not find this in the cited paragraphs. Alberte has nothing to do with the subject matter of Kim or Bochner.

In any event, Alberte really adds nothing to the combined teachings of Kim and Bochner. As the Examiner has correctly observed, Kim suggests preventing adhesion to the first and second layers so that cells are not damaged when these layers are removed. It alternatively suggests not preventing adherence so that cells which are damaged by removal of the first and second layers can be observed. Either way, however, cells must not be prevented from adhering to Kim's substrate, and must not be prevented from migrating as recited in claim 1 or Kim will not function for its intended purpose. Therefore, no combination of the teachings of Kim and Bochner, in light of Alberte (or even disregarding Alberte) would be obvious to a person having ordinary skill in the art will meet the terms of claim 1, and claim 1 should be allowed.

Claims 2, 3, 6, 7, 12, 18, 22, 27, 29, 35, 42, 43, 48, 49, 56, 68, 74, 86, 90, 91, and 195-199 are all directly or indirectly dependent on claim 1, and should be allowed for the same reasons as above.

Claim 121 was rejected as unpatentable Kim in view of Bochner in light of Alberte. As now presented in independent form, claim 121 recites:

A method of making a chip-device for holding living cells, including a plurality of wells, each well configured to hold a living cell, and a carrier for said wells, the wells being located on or in said carrier, the method comprising:

- (a) providing a template having negative of features of said carrier;
- (b) contacting said template with a precursor material so as to create said features in said precursor material;

(c) fixing said features in said precursor material so as to fashion said carrier; and

(d) configuring said wells to prevent migration or loss of cells therein during storage, movement, testing and observation, and to inhibit or delay adhesion thereto of living cells held in said wells.

Clause (d) is derived from now canceled claim 145.

As noted above, the Examiner has acknowledged that Kim contains no disclosure, teaching, or suggestion of configuring the wells to prevent migration or loss during observation, or to inhibit or delay adhesion.

Bochner's wells are standard, and the gel inside the wells adheres the cells to the wells. The Examiner argues that the cells in Bochner do not adhere to the wells, but this is not correct. The cells adhere to the wells in the same way that pieces of fruit in a bowl of Jell-O® adhere to the bowl, or that something glued to a surface adheres to the surface. Claim 121 is allowable for all these reasons.

Claims 130, 132, and 139 are dependent on claim 121 and should be allowed for the same reasons.

Independent claims 186, 193, 200, and 205 have also been rejected as unpatentable over Kim in view of Bochner in light of Alberte. These rejections are respectfully traversed.

Independent claim 186 recites:

A method of growing cells comprising:

(a) providing a well-bearing device;

(b) holding at least one living cell in a well of said well-bearing device; and

(c) increasing the size of said well so as to provide an increased space for proliferation of said cell.

The Examiner refers to Kim as teaching expandable wells, but applicant fails to find even a suggestion of this. If the Examiner adheres to this rejection, she is respectfully requested point out where in Kim this feature is taught.

Independent claim 193 recites a well-bearing device having a plurality of protuberances protruding from a surface of the well-bearing device, and calls for

contacting the biological sample with said surface so as to remove cells from the biological sample.

This rejection is not understood. The Examiner appears to be equating Kim's layers 150 and 160 with the recited protuberances, but there does not appear to be any basis for this. Suffice to say that according to Kim, cells are not removed until layers 150 and 160 have been peeled away. Apart from the deficiencies in Kim, Bochner and Alberte demonstrated above, claim 193 is allowable for this additional reason.

Dependent claim 194 is allowable for the same reasons as claim 193.

Independent claim 200 is directed to a device for holding living cells in which the wells delay or inhibit adhesion thereto or proliferation therein of cells inside said wells. These features have been discussed at length above, and claims 200 and 205 are allowable for all the reasons previously adduced. Claims 201-204, dependent on claim 200 and claims 206-213, dependent on claim 205 are allowable for all the same reasons.

All of the other claims have been rejected as being unpatentable over Kim in view of Bochner in light of Alberte (hereafter, "the basic combination") in light of other references, as discussed below.

Claims 18, 22, 27, 29, 153, 178, 179, and 181 have been rejected as unpatentable over the basic combination, further in light of Ravkin U.S. published application 2003/0059764 (Ravkin). The Examiner relies on the rejection of claim 1, which has been demonstrated above to be improper. Ravkin does nothing to remedy the deficiencies in the basic combination. Examiner has cited Ravkin for its teaching of what she interprets the "outer layer" mentioned in paragraph [0090] as being a gel cover. The Examiner's interpretation is overly expansive. Ravkin does not suggest a cover. His outer layer is just part of the well structure.

A person having ordinary skill in the art would not put a gel in Kim's wells for the reasons discussed above. In any event, there is nothing in Ravkin to suggest the gel should be removed once placed in the wells, or even that it is removable.

It is further noted that the Examiner has taken the position, in her discussion of purported intended use limitations, that the structure shown by the combination of Kim, Bochner, Alberte and Ravkin is the same as that described in the rejected claims and is capable of performing the same functions. In the analysis of claim 1 above, it has been amply demonstrated that the Examiner's position in this regard is not correct.

The discussion of intended use seems irrelevant, in any event. None of these claims recite intended use. The apparatus claims speak about the configuration of the

recited elements. These are recitations of structure. Method claim 153 likewise does not recite intended use, but rather specific method steps.

Claims 178, 179, and 181 are dependent on claim 153 and should be allowed for the same reasons.

Claims 12, 90, 91, and 198 have also been rejected as unpatentable over Kim in view of Bochner in light of Alberte and further in light of Sanghera U.S. patent 5,525,800 (Sanghera) in light of Hahn U.S. published application 2003/0017079 (Hahn).

In these rejections, the Examiner specifically relies on the rejection of claim 1, on which these claims depend. However, the rejection of claim 1 has been demonstrated above to be improper. Sanghera and Hahn add nothing to overcome the deficiencies in the basic combination, and in any event are relied on by the Examiner only for their discussion of index of refraction. Claims 12, 90, 91, and 198 are all allowable over the basic combination in light of Hahn and/or Sanghera for the same reasons as claim 1.

Claims 18, 22, 27, 29 are all dependent on claim 1. These claims are allowable for all the same reasons as claim 1 and for the additional reason stated immediately above.

Claims 210-213 have been rejected as unpatentable over the basic combination further in view of Oldenburg et al. U.S. patent 6,027,095 (Oldenburg). These claims are dependent on claim 205 and are also allowable for the same reasons discussed above in connection with claim 205.

Preliminarily, the Examiner appears to have referred to Kim for *in situ* gelling. In fact the teaching in question is in Bochner. It has been demonstrate above that a person having ordinary skill in the art would not use Bochner's gel in Kim's device as it would destroy Kim's utility for its intended purpose.

The Examiner relies on Oldenburg for its teaching that vapor deposition can be used for coating the insides of wells in a microtiter plate. That may be, but it certainly does not overcome the basic deficiency in the basic combination. Claims 210-213 are allowable no matter what is disclosed, taught or suggested in Oldenburg.

In view of the foregoing amendments and arguments, it is respectfully submitted that the application is in condition for allowance, and early notice thereof is respectfully solicited.

Respectfully submitted,

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Enclosed:

- Petition for Extension (One Month)